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Review Article

OVERDOSE RISK OF VITAMINS: A REVIEW

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ABSTRACT

Vitamins are the organic substances which are very essential for the biological process of life. Insufficient vitamins in the body leads to decreased biological capabilities of body, which may cause various serious health problems. The requirement of vitamins in body is fulfilled by the nature while the supplementary intake of vitamins causes toxicity in body. Vitamins deficiencies is a common problem in the people of developing countries. Vitamins and dietary supplements are readily available in different formulations in wide variety of retail outlets without any regulations. In the recent years there has been a great increase on interest about hypervitaminosis, the intoxication resulting from an excess intake of vitamin. Hypervitaminoses are primarily caused by fat-soluble vitamins (D and A), as these are stored by the body for longer period than the water-soluble vitamins. Hypervitaminosis is a uncommon but serious form which is manifested after mega dose substitute in addition to other sources as well. The management primarily focuses on reduced dietary intake with proper attention to hydration along with discontinuation of vitamin therapy. In this study authors are trying to focus in the urgent attention on toxicity of vitamins and unwanted uses of vitamins in daily life.

KEYWORDS: Vitamins, toxicity, overdose, hypervitaminosis, adverse effects, fatal

INTRODUCTION

To weigh the pros and cons of dietary supplements requires a fairly basic understanding of the role of the immune system. Thoughtful supplementation also requires an understanding of evidence about safety and effectiveness, dosing issues, and the law relating to supplements.[1]

Dose is a critical factor with any medication or supplement, and more is not always better. Supplements may have different effects depending on the size of the dose that is taken. While a small amount of certain supplements may be useful, larger amounts may be dangerous. Proper dose should always be considered before beginning supplementation.[2]

Absence of Regulation

In the United States, supplements are not regulated in the same rigorous way as medications are. Before being marketed, medications must undergo controlled clinical trials that demonstrate their effectiveness and safety for the treatment of particular medical conditions. This is in sharp contrast to dietary supplements (Manufacturers of supplements are not required to prove the effectiveness of their products or accurately report what is contained in them). As a result, supplements may contain varying amounts of the active ingredients of variable quality.

In the United States, nearly half of the adult population takes some form of multivitamin or mineral supplement. What makes this level of consumption all the more curious is that most of the users are not taking the supplements because they feel ill or exhibit symptoms of vitamin deficiencies. Rather, it seems to be based on the idea that if a little bit of something is good, then more is better. Most of the vitamins and minerals we need to remain healthy are only necessary in small amounts. *So, do multivitamins work?*

Vitamins

Vitamins are defined as organic matter necessary in little quantity for the maintenance and development of living organisms. Vitamins are vital micronutrients, which desires in little amounts for the variety of roles in body. Vitamins are divided into two groups: water-soluble (B-complex vitamins and vitamin C) and fat-soluble vitamins (A, D, E and K).

Functions and Categories

Vitamins have a variety of functions that help to control metabolism, to prevent chronic diseases (such as heart disease and cancer), and to keep normal appetite, mental health, and immunity. Vitamins can basically be classified into the following two categories:

1. Fat-soluble vitamins: comprise Vitamins A, D, E and K; dissolve in fats; and are absorbed with the aid of fats that are in the diet. Excessive fat-soluble vitamins are stored in the liver and will not be eliminated from the body.
2. Water-soluble vitamins: comprise Vitamins B and C, and dissolve in water. Excessive amount of water-soluble vitamins are excreted through urine and sweat.[3]

The quantity of vitamins in food is affected by the ways in which food is stored or cooked. Vitamins A and C, and some vitamins B can be damaged under strong light, so food rich in those vitamins should be stored in dark places. Vitamin C and some Vitamins B are soluble in water and can be destroyed in high temperature, and therefore we should avoid wash them too much and cooked them too long time.[3] Vitamins do not give energy and

they cannot be used without any sufficient supply of fats, carbohydrates, proteins and even minerals. Fat soluble vitamins (Vitamin A, C, D, E, K) are different from water soluble vitamins (B, C), mainly as larger amount can be stored in the body. Vitamin A and vitamin D are stored for extended period of time; therefore, negligible shortage may not be recognized until extreme reduction has occurred.[3,4]

Fat Soluble Vitamins

Vitamin A

The term 'vitamin A' is used to refer to retinol and related compounds that show the biological movement of retinol. The main forms of vitamin A are retinol, retinoic acid and retinal, while the main liver storage form is retinyl palmitate. Retinoic acid is thought to be necessary for embryonic stem cell differentiation and development, and in maintaining healthy configuration and function of epithelial cells.

Different dietary sources of vitamin A have different potencies. For example, beta-carotene is less easily absorbed than retinol and must be converted to retinal and retinol by the body. One of the new international values of measure for vitamin A is retinol activity equivalent (RAE), which represent vitamin A activity as retinol. [5]

Requirements of vitamin A and carotenoids

In most societies, vitamin A requirements are met by the collective utilization of carotenoid precursors of vitamin A in plants and preformed vitamin A (retinol and retinyl esters) in animal foods. There has been no consensus in different countries as to the quantity of vitamin A and carotenoids that should be consumed in order to preserve optimal health. Whereas no recommendation are generally given for carotenoids, most countries have based their recommendation between 500 and 1,000 µg of retinol equivalents (RE) for adults.[6] Much of the world relies on WHO and the Food and Agriculture Organization (FAO) to publish and circulate the technical information that is used for national dietary allowances or as a basis for producing national nutrient requirement standards. The establishment of human nutrient requirements is a precondition for countries to expand food-based dietary strategy for their populations. During the 1980s, WHO and FAO reviewed the literature on vitamin A requirements. However, growth in vitamin A study as then requires updating knowledge of the subject. WHO and FAO are now in the practice of revising their recommendations.[7]

The toxicity of vitamin A occur as acute and chronic

In acute cases the features of hypervitaminosis are mostly due to exaggeration of their normal physiological and biochemical actions. Features in acute case are faintness, headache, and lassitude, irritability, pain abdomen, nausea, visual disturbances like diplopia, and bulging fontanels in infants, pruritus and excoriation of skin all over the body. Chronic cases are manifested by low grade fever, alopecia, dry fissured lip, ache in bones and joints, hyperostosis, anorexia, weight loss, hepatosplenomegaly, papilloedema, pseudotumour cerebri, if daily 25,000 IU or more vitamin A is consumed for many days. Other features suggestive of raised intracranial pressure, such as bulging fontanels (in an infant), papilloedema and diplopia, may also occur. Anemia and thrombocytopenia have also been described.

Complications include: Hypocalcaemia, Hypercalciuria and renal stones. It may be foolish to give vitamin A supplements to older patients with good diets, mainly if at danger of osteoporosis.[8]

The minimum daily supplement connected with liver cirrhosis that has been reported is 7500 mg taken for 6 years .Very elevated solo dose can also cause brief acute lethal symptoms that may comprise bulging fontanelle in infants; headaches in big children and adults; and nausea, diarrhea, loss of hunger, and irritability in all age groups. Rarely does toxicity occur from eating of food sources of preformed vitamin A. When women take vitamin A at daily levels of more than 7500mg (25000IU) during the early stages of gestation, fetal anomalies and poor reproductive outcomes are reported. [8]

Infants, including neonates[9] administered single doses equivalent to 15000–30000 mg retinol (50000–100000IU) in oil generally show no adverse symptoms. However, daily prophylactic or therapeutic doses should not exceed 900mg, which is well above the mean requirement of about 200mg/day for infants. An increase in bulging fontanelles occurred in infants under 6 months of age in one endemically deficient population given two or more doses of 7500mg or 15000mg preformed vitamin A in oil [10,11] but other large-scale controlled clinical trials have not reported increased bulging after three doses of 7500mg given with diphtheria-pertussis-tetanus immunizations at about 6, 10, and 14 weeks of age.[11]

Sawsan H Mahassni investigates the effects of vitamin A administration above dietary requirements on some cells of the immune system in healthy male rats. A 105 male Wister rats were divided equally into three groups (control and two experimental). Test groups were orally administered with vitamin A at two different concentrations (8,000 and 15,000 IU/kg body weight) for 21 days, while the control group was not administered with vitamin A. Blood samples were collected from all rats and assayed for the different cells and antibodies. Compared to their respective controls, total white blood cells and neutrophil counts were significantly improved, while the basophil and total lymphocyte counts were decreased after low dose vitamin A administration.[12]

Vitamin D

Vitamin D (calciferol) comprise a collection of fat soluble seco-sterols originate naturally only in a small number of foods, such as fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. The two main physiologically important form of vitamin D are D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_3 is photosynthesized in the skin of vertebrates by the action of solar ultraviolet (UV) B radiation on 7-dehydrocholesterol. Vitamin D_2 is produced by UV irradiation of ergosterol, which occurs in molds, yeast, and higher-order plants. Under situation of regular sun exposure, dietary vitamin D intake is of minor importance.[13] However, latitude, season, aging, sunscreen use, and skin pigmentation control the production of vitamin D_3 by the skin. Most of the nutritional intake of vitamin D comes from fortified milk products and other fortified foods such as breakfast cereals and orange juice. Both vitamin D_2 and D_3 are used in non-prescription vitamin D supplements, but vitamin D_2 is the form existing by prescription in the United States.[13]

The enzyme accountable for the conversion of 25[OH] D to its biologically active form [Vitamin D (1,25$[OH]_2$ D)] has been known in other tissues aside from kidneys and that extra renal blend of 1,23$[OH]_2$D may be regularly significant in variable cell growth and separation via paracrine or autocrine regulatory mechanisms.

There are three major hypothesis for vitamin D toxicity:

(i) Raised plasma 1,25[OH]D concentration lead to enlarged intracellular 1,24[OH]D concentrations. This assumption is not generally supported as abundant studies exposed that vitamin D toxicity is connected with usual or slightly high 1,25[OH]D.[14]

(ii) Vitamin D intake raise plasma 25[OH]D levels to concentration that exceed DBP binding capacity, and free 25[OH]D has straight effects on gene expression once it enters target cells. High dietary vitamin D intake alone increases plasma 25[OH]D. The low affinity of 1,25[OH]D for the transport protein DBP and its high resemblance for VDR control normal working. This makes it the only ligand with access to the transcriptional signal transduction machinery. However, in vitamin D intoxication, congestion by a variety of vitamin D metabolites considerably compromises the capacity of the DBP by allowing other metabolites to enter the cell nucleus. Of all the inactive metabolites, 25[OH]D has the strongest affinity for the VDR, and thus at sufficiently high concentrations, could stimulate transcription.

(iii) Vitamin D intake raises the concentration of many vitamin D metabolites, including vitamin D itself and 25[OH]D, and these concentrations exceed the DBP binding capacity and free of "free" 1,25[OH]D which enters target cells.[14]

Daily Dose of Vitamin D

Current US Daily Reference Intakes (DRI) for vitamin D are:

- Infants 0-12 months, 200 IU (5 mcg)
- Males and females 1-50 years, 200 IU (5 mcg) 51-70 years, 400 IU (10 mcg) 71 years and older, 600 IU (15 mcg)
- Pregnant or nursing women, 200 IU (5 mcg)[15]

Clinical Features of Vitamin D Toxicity

The clinical manifestation of hypervitaminosis D is varied and mostly consequences from hypercalcemia and reflect the necessary role of calcium in many tissues and targets, including bone, cardiovascular system, nerves and cellular enzymes. Initial signs and symptoms of hypervitaminosis D may be comparable to other hypercalcemic states and include generalized weakness and weight loss. Central nervous system features may include confusion, difficulty in concentration, drowsiness, apathy and coma. Neuropsychiatric symptoms include depression and psychosis, both of which are resolved following improvement of the hypercalcemia. Hypercalcemia can influence the gastrointestinal tract and cause regular vomiting, abdominal pain, polydipsia, anorexia, and constipation.[15]

Parvaiz A. Koul studied that physicians often treat patients with high doses of vitamin D for various ailments and on occasion the prescribed doses far exceed the requirements of the patients. Ten cases of hypercalcemia due to vitamin D intoxication are presented with features of vomiting, polyuria, polydipsia, encephalopathy and renal dysfunction.[16]

Anil Kumar Gupta studied that clinical features of hypervitaminosis D are varied and mostly due to hypercalcemia. A patient may present with fatigue and weight loss, recurrent vomiting, abdominal pain, polydipsia, anorexia, constipation.[17]

Vitamin E

Vitamin E is a fat-soluble vitamin, necessary for health. It can be stored by the body, so vitamin E does not have to be consumed every day. Good source are vegetable oils, nuts and nut oil seeds, egg yolk, margarine, cheese, soya beans, wheat germ, oatmeal, avocados, olives, green leafy vegetables, etc. Tocopherols are predominant in olive, sunflower, corn, soya beans oils, and tocotrienols are the major vitamin E components of palm oil, barley and rice bran.[18]

Vitamin E doses used in antioxidant treatment may arouse justified concerns because, for example in the United States, 300 mg/d is the most tolerated daily dose of this vitamin, and 2 g/d is already measured to be toxic. High doses of vitamin E reduce systemic vitamin A stores and when administer in the α-tocopherol or its acetate form, they limit the dietary absorption of therapeutically important γ-tocopherol, present only in the diet. Vitamin E anticoagulant action cause its antagonism with vitamin K, which can lead to bleeding when the latter is lacking, particularly in patients treated with anticoagulants (e.g. with acenocoumarol or warfarin) or estrogens – both groups should not be given more than 40 mg/d of vitamin E. The injurious effects of vitamin E were also observed after it had been applied in the treatment of coronary artery disease treated with simvastatin and niacin (i.e. nicotinic acid).[19]Evidence of pro-oxidant damage has been associated with the feeding of supplements but usually only at very high doses (e.g. >1000mg/day).Nevertheless, the recent report from the Netherlands of increased severity of respiratory tract infections in persons over 60 years who received 200mg vitamin E per day for 15 months, should be noted in case that is also an indication of a pro-oxidant effect.[20]

Vitamin K

The term vitamin K represent a collection of chemically similar fat-soluble compounds that differ in their origin and/or function. There are two naturally occurring forms of vitamin K: Vitamin K_1 and Vitamin K_2. Vitamin K_1, also called phylloquinone or phytonadione, is synthesized by plants and is the main form of vitamin K in the human diet. Major dietary sources of phylloquinone are green leafy vegetables (e.g., kale, parsley), vegetables in the Brassica genus (e.g., Brussels sprouts, broccoli), some fruits (e.g., avocado, kiwi, and green grapes), some herbs (e.g., parsley and cilantro), and green and herbal teas. Additional dietary sources are plant oils such as soybean, canola, and olive oils. Phylloquinone from green, leafy vegetables is strongly bound to the plant cell membranes and is less bioavailable than the phylloquinone present in plant oils or dietary supplements. [21]
Naturally both phylloquinone and menaquinone are non-toxic in nature however adverse effects such as haemolytic anaemia, jaundice, anaphylactic reactions are noticed in premature infants when taken in excess amounts. [22],[23] Synthetic forms of vitamin K and menadione are more toxic than naturally occurring forms. Injections of menadione harm the cell membranes by oxidation of glutathione. [24,25, 26]

Vitamin B

The Vitamins B are thiamine (B_1), riboflavin (B_2), niacin (B_3, also called nicotinamide or nicotinic acid amide), pantothenic acid (B_5), pyridoxine (B_6), biotin (B_7), folic acid or folate (B_9) and cobalamin (B_{12}).

Vitamin B_1

Thiamine was the first B vitamin to have been recognized, thus its designation is B_1. Thiamine occur in the human body as free thiamine and as a variety of phosphorylated forms: thiamine monophosphate, thiamine triphosphate, and thiamine pyrophosphate, which is also recognized as thiamine diphosphate. Thiamine plays a central role in cerebral metabolism. The brain uses glucose as a major fuel for energy generation. Glucose enters the brain by diffusion across the blood–brain barrier. About 30%

of the glucose absorbed by the brain undergo a complete oxidation through the Krebs cycle.

There is no toxicity observed by vitamin B_1. Thiamine toxicity is not a problem because renal clearance of the vitamin is rapid.[27, 28]

Vitamin B_2 (Riboflavin)

Riboflavin (vitamin B_2) deficiency results in the condition of hypo- ariboflavinosis, with sore throat; hyperemia; edema of the pharyngeal and oral mucous membranes; cheilosis; angular stomatitis; glossitis; seborrheic dermatitis; and normochromic, normocytic anaemia.[29] The major cause of hyporiboflavinosis is inadequate dietary intake as a result of limited food supply, which is sometimes exacerbated by poor food storage or processing. Children in developing countries will commonly demonstrate clinical signs of riboflavin deficiency during periods of the year when gastrointestinal infections are prevalent.

Toxicity

Riboflavin toxicity is not a problem because of limited intestinal absorption.

Vitamin B_3 (Niacin)

The recommended dietary intake of niacin is 14 to 16 mg per day. In pharmacological doses for hyperlipidemia (1 to 4.5 g/day depending on the preparation), common side effects of niacin are flushing, nausea, vomiting, pruritus, hives, mild elevation in serum amino transferases and constipation. A niacin-induced myopathy has also been described with therapeutic doses. Caution should be used in patients with a history of gout due to elevations in uric acid. When less than 1 gram/day of niacin is ingested, only a handful of anecdotal cases of toxicity have been reported in the literature. Two acute oral studies in rats were available yielding slightly different results. In the first study an LD_{50} value of about 3.5 g/kg bw was reported for both male and female animals. Effects were tremor and convulsions, sedation, and coma. In the other study a value of 7.1 g/kg bw was found for males and 5.5 g/kg bw for females. Clinical symptoms included ruffled coat, lethargy and coma. The oral LD_{50} in mice reported in a study was 3.1 g/kg bw. Loss of activity was observed in high dose animals within 60 minutes after dosing. Survivors were asymptomatic within 24 hours. Other data from the literature for nicotinamide administrated orally to mice and rats indicated LD_{50} values between 2.0 and 3.0.[30,31]

Vitamin B_6

Animal studies have revealed that vitamin B_6 is potentially neurotoxic, causing peripheral neuropathy, with ataxia, muscle weakness and loss of balance in dogs given 200 mg pyridoxine/kg body weight for 40–75 d, and the growth of a swaying gait and ataxia within 9 days at a dose of 300 mg/kg body weight. At the lower dose of 50 mg/kg body weight there are no clinical signs of toxicity, but histologically there is loss of myelin in dorsal nerve roots. At higher doses there is extensive neuronal damage, with loss of myelin and degeneration of sensory fibers in peripheral nerves, the dorsal columns of the spinal cord and the descending tract of the trigeminal nerve. The clinical signs of toxicity after 200–300 mg vitamin B_6 /kg body weight regress within 3 months after the removal of these huge doses. At even higher doses (500 or 1000 mg/kg body weight by intraperitoneal injection) pyridoxine has been revealed to cause a reduce in testis weight, histological changes in the testes and reduced spermatogenesis and sperm motility.[32]

Use of high doses of pyridoxine for the treatment of pre-menstrual syndrome, carpal tunnel syndrome, and some neurologic diseases has resulted in neurotoxicity.

Vitamin B_{12}

Vitamin B_{12} has been connected with the growth of age-related macular degeneration (AMD) and risk of frailty, both leading causes of disability in the elderly. AMD is the most important reason of vision loss in the elderly. Risk factors include increasing age, family history, hypertension, smoking, obesity, sunlight exposure and hypercholesterolemia.[33]

Saleem Ali Banihani demonstrate the optimistic effects of vitamin B_{12} on semen quality: first, by rising sperm count, and by enhancing sperm motility and falling sperm DNA damage, though there are a few *in-vivo* systems studies that have deliberated some undesirable effects. The beneficial effects of vitamin B_{12} on semen quality may be due to enlarged functionality of reproductive organs, decrease homocysteine toxicity, reduced amounts of generated nitric oxide, decrease levels of oxidative damage to sperm, reduced amount of energy produced by spermatozoa, decreased inflammation-induced semen impairment, and control of nuclear factor-κB activation.[34]

Vitamin C

Although intake of high doses of vitamin C is supposed to be harmless, based on that it is a water-soluble vitamin and is not stored in the body, there are numerous side effects and drug interactions reported in the literature. It has been reported that high-dose vitamin C could enlarge hemolytic anemia in those who have Glucose-6-phosphate dehydrogenase deficiency; and the risk of renal failure in those who have renal disorders. In addition, as vitamin C may enlarge the bioavailability of iron, its use in hemochromatosis patients is not recommended. Since vitamin C acidifies the urine, it can cause the development of kidney stones; and on the other hand, a case of hyperoxaluria may appear due to oxalic acid formed as a result of vitamin C metabolism.[35]

Seyeon Park studied the effect of high doses of vitamin C for the treatment of cancer has been controversial. Previous studies reported that vitamin C at concentrations of 0.25–1.0 mM induced a dose- and time-dependent inhibition of proliferation in acute myeloid leukemia (AML) cell lines and in leukemic cells from peripheral blood specimens obtained from patients with AML. Treatment of cells with high doses of vitamin C result in an immediate increase in intracellular total glutathione content and glutathione-S transferase activity that was accompanied by the uptake of cysteine.[36]

Table 1: Recommended daily intakes of various food supplements[37]

Vitamins	Recommended daily intake	Over dosage (mg or µg/d)
Vitamin A	600 µg	Extremely high doses (>9000 mg) can cause dry, scaly skin, fatigue, nausea, loss of appetite, bone and joint pains and headaches
Vitamin B_1 (thiamin)	1,4 mg	No toxic effects resulting from high doses have been observed
Vitamin B_2 (riboflavin)	1,6 mg	Doses higher than 200 mg may cause urine color alteration
Vitamin B_3 (niacin)	18 mg	Doses larger than 150 mg may cause problems ranging from facial flushing to liver disease
Vitamin B_5 (pantothenic acid)	6 mg	Dose should not exceed 1200 mg; this may cause nausea and heartburn
Vitamin B_6 (pyridoxine)	2 mg	Doses larger than 100 mg may cause numbness and tingling in hands and feet
Vitamin B_{12} (cobalamin)	6 µg	Doses larger than 3000 µg may cause eye conditions
Vitamin C (ascorbic acid)	75 mg	No impacts of over dose have been proven so far
Vitamin D (cholecalciferol)	5 µg	Large doses (>50 µg) obtained from food can cause eating problems and ultimately disorientation, coma and death.
Vitamin E (tocopherol)	10 mg	Doses larger than 1000 mg cause blood clotting, which results in increased likelihood of hemorrhage in some individuals
Vitamin K	80 µg	Large doses of one form of vitamin K (menadione or K_3) may result in liver damage or anemia

CONCLUSION

Intake of vitamins and dietary supplements in developing countries is very common. Generally fat-soluble vitamins (vitamin A and D) cause vitamin toxicity due to the longer depositions and very slow pharmacokinetic in the body. The people of such countries are using vitamins without thinking their side effects. At the end, the hypervitaminosis is rare but it causes health hazards. The irrational use of vitamins leads to various health issues and problems in humans, so we have to avoid the overdose and misuse of vitamins.

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